

EDITORIAL COMMENT

In-Laboratory High-Dose Clopidogrel Loading

Do We Need a Mirror of Diamond for “Armida’s Garden”?*

Goran Stankovic, MD, PhD,
Milorad Zivkovic, MD
Belgrade, Serbia

Dual antiplatelet therapy, which consists of aspirin and clopidogrel, forms the cornerstone of pharmacotherapy following percutaneous coronary intervention (PCI) with the goal of reducing stent thrombosis, as well as ischemic events related to the underlying coronary artery disease. The effects of clopidogrel on patient outcomes have been widely investigated in clinical studies that have involved a range of treatment regimens. When administered without a loading dose, clopidogrel 75 mg daily causes maximal inhibition of platelet aggregation after 3 to 7 days (1). One way to increase the generation of the active metabolite of clopidogrel is to raise the dose of the drug, and several trials have established the benefit of pre-treatment with clopidogrel in PCI (2–5). The PCI-CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial showed that

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pre-treatment with clopidogrel (300-mg loading dose, followed by 75 mg daily) in addition to aspirin for a median of 10 days before PCI, compared with aspirin alone, reduced primary end point by 30% after 1 month (2). Furthermore, a post-hoc analysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial has demonstrated that for clopidogrel to be fully effective, the loading dose of 300 mg of clopidogrel should be given at least 15 h before intervention (3). Although this dose can be readily implemented in patients undergoing elective PCI, it is problematic when unplanned intervention is required in an urgent setting. A higher loading dose with 600 mg of

clopidogrel causes an earlier and stronger platelet inhibition than the 300-mg dose, and the results of the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment) trial and ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) trial suggest that if a 600-mg loading dose is chosen, no advantage is gained by increasing the pre-treatment duration beyond 2 h (4,5). Increasing the dose to 900 mg has been associated with marginal increases in the magnitude and speed of platelet inhibition, but significant differences between the 600- and 900-mg doses have not been demonstrated (5). Thus, regardless of the size of the loading dose, pharmacodynamic studies indicate that 2 h is the minimum pre-intervention interval that is necessary to achieve optimal inhibition of platelet aggregation with clopidogrel. This apparent threshold in the pharmacodynamic effect of clopidogrel has been attributed to limited intestinal absorption of the drug, variability in cytochrome P450-dependent enzyme activity and drug–drug interactions (1). Based on available clinical evidence, American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions 2009 focused updates of guidelines on PCI recommend that at least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI (6). The European Society of Cardiology guidelines recommend that a 300-mg loading dose of clopidogrel should be administered at least 6 h before PCI (7). Physicians must take these recommendations into consideration while simultaneously dealing with the realities of clinical practice.

Yet, in a “real-world” setting, only very few patients are actually scheduled for elective PCI, whereas most patients are scheduled for elective diagnostic coronary angiography (CAG) with immediate “ad hoc” PCI procedure when indicated. Although not formally approved (although routinely used in many centers worldwide) 2 pre-loading strategies have been proposed to overcome this problem: first, pre-loading with clopidogrel of all patients undergoing diagnostic CAG (thus, unnecessarily exposing the majority of patients without indication for PCI to aggressive antiplatelet medication and potentially causing avoidable bleeding complications), or second, in-laboratory (“in-lab”) clopidogrel administration after diagnostic angiography, when anatomy is known and indication for PCI established, but when optimal “antithrombotic status” is not achieved. This strategy was tested in the recent randomized PRAGUE-8 study in which 1,028 patients submitted to diagnostic CAG were randomized to receive a 600-mg clopidogrel loading dose more than 6 h prior to the procedure (mean interval was 20 h) versus a 600-mg loading dose given in-lab at the time of PCI following angiography (8). Importantly, only 29% of the initial cohort underwent PCI after angiography. High-dose clopidogrel before elective angiography in-

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From the Clinic for Cardiology, Department for Diagnostic and Catheterization Laboratories, Clinical Center of Serbia, Medical School of Belgrade, Belgrade, Serbia. Dr. Stankovic is supported by a grant from the Ministry of Science of the Republic of Serbia. Dr. Zivkovic reports that he has no relationships to disclose.

creased the risk of minor bleeding complications (although bleeding risk in the pre-load group of 6.5% appears to be excessive considering the elective nature of the procedures), whereas the effect on the primary ischemic end point was not significant (1.3% vs. 2.8%; $p = 0.43$). The authors conclude that in patients with chronic stable angina, clopidogrel can be administered safely in the catheterization laboratory before “planned elective PCI” as well as before “ad hoc” PCI, but not before “planned elective diagnostic coronary angiography.” Importantly, the sample size of this study was underpowered to detect differences in clinical outcome in the 298 patients undergoing PCI.

In this issue of the *Journal*, the main results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial are presented by Di Sciascio et al. (9).

Armida is a beautiful enchantress in Torquato Tasso’s epic poem “Jerusalem Delivered,” who bewitched Rinaldo, one of the Crusaders, in a maze in Armida’s garden. The spell is broken by a mirror of diamond that 2 Christian knights give to Rinaldo, and his warlike spirit is rekindled when he glimpses his reflection and decries what has become of him (10).

In the ARMYDA-5 trial, a total of 409 patients were randomized to receive a 600-mg clopidogrel loading dose 4 to 8 h before PCI (pre-load group) versus a 600-mg loading dose given in the catheterization laboratory after CAG, but prior to PCI (in-lab group); primary end point was 30-day major adverse cardiac events (MACE) incidence. The authors found no significant difference in the primary end point between the 2 arms (8.8% in-lab vs. 10.3% pre-load; $p = 0.72$), and no significant increased risk of bleeding/vascular complications was observed in the pre-load arm (5.4% vs. 7.8%; $p = 0.42$). The trial addresses a clinically relevant question with a randomized controlled trial, and the results support the in-lab administration of clopidogrel as a safe alternative to routine pre-treatment given before knowing a patient’s anatomy.

These observations are interesting and provocative, although some points from ARMYDA-5 trial are worth highlighting.

First, ARMYDA-5 enrolled a mixed patient population, including consecutive patients with both stable angina (60%) and acute coronary syndrome (ACS) (40%), and consequently, a small number of patients was enrolled in each group. Although the MACE rate was similar for the total population (8.8% in-lab group vs. 10.3% pre-load group), there was a 60% increase in the MACE rate in ACS patients (16%), which could have reached statistical significance if the number of patients enrolled was higher. Since the MACE rate in patients with stable angina using in-lab loading was 5%, it seems that events in the in-lab group are mainly driven by the ACS group (in fact, early platelet inhibition is mandatory in such patients due to the elevated thrombotic risk, and a full antiplatelet effect in the case of “ad hoc” PCI is desirable and recommended by guidelines). However, subgroup analysis was performed post

hoc, not as a pre-specified end point, and unidentified factors may exist that explain why patients with ACS had higher event rates. Thus, further studies are needed before concluding that in-lab clopidogrel administration is adequate in all cases regardless of clinical presentation.

Second, the results of ARMYDA-5 are somewhat controversial because there is no relationship between clinical outcomes and higher platelet reactivity as assessed by VerifyNow P2Y₁₂ assay (Accumetrics Inc., San Diego, California) during PCI and during the “critical” 2 h after PCI. This may represent either a small sample size (resulting in relatively small numbers of events) to determine clinical differences in relation to platelet reactivity assessment or the lack of usefulness of this point-of-care measurement in clinical practice. The difference of P2Y₁₂ reaction unit values at the time of PCI reflects the different timing of clopidogrel loading in the 2 groups; if platelet reactivity is truly higher in the in-lab group, the concern may arise, and a larger trial powered specifically to early stent thrombosis may be required. Nevertheless, this study serves the purpose of stimulating more and larger efforts to study the issue of clopidogrel platelet reactivity by developing either new regimens of the same drug or new drugs that have different, more predictable, and more powerful effects on platelet function, such as prasugrel or ticagrelor. With these new compounds, it may no longer be necessary to consider pre-treatment, because of more rapid onset and more pronounced platelet inhibition than clopidogrel.

Taking into account those limitations, we cannot resist asking ourselves whether we need our own mirror of diamond to unravel all the secrets from Armida’s garden.

Reprint requests and correspondence: Dr. Goran Stankovic, Clinic for Cardiology, Department for Diagnostic and Catheterization Laboratories, Clinical Center of Serbia, 8 Koste Todorovica, 11000 Belgrade, Serbia. E-mail: gorastan@sbb.rs.

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